Subjective and objective cancer-related cognitive impairment in chronic lymphocytic leukemia

Senior Research Thesis

Presented in partial fulfillment of the requirements for graduation *with research distinction* in Psychology in the undergraduate colleges of The Ohio State University

by

Marcia F. Burns

The Ohio State University

April 2018

Project Advisor: Dr. Barbara Andersen, Department of Psychology

Abstract

Introduction: Cancer-related cognitive impairment (CRCI) or chemo-brain refers to impairment across domains of executive functioning amongst cancer patients. Cognitive impairment has been reported in patients before, during, and after treatment and is associated with a reduction in quality of life. The current study using a prospective longitudinal study design. examines the cognitive effects of a novel immunotherapy in chronic lymphocytic leukemia (CLL) patients, an under-represented cancer group in CRCI literature.

Method: Forty-four (44) patients with CLL were assessed at pre-treatment, and upon 6 months, and 12 months of receiving treatment in a phase II trial of obinutuzumab, venetoclax, and ibrutinib immunotherapy. Cognition was assessed through recommended subjective, self-report and objective, neuropsychological assessments: Patient-Reported Outcomes Measurement Information System: Cognitive Function (PROMIS-CF), NIH Auditory Verbal Learning Test (AVLT), and Controlled Oral Word Association Test (COWAT). Independent-samples t-tests and linear mixed models examined effects of prior treatment history, time, and potential moderating covariates (e.g. age, and symptoms of depression and anxiety).

Results: Cognitive impairment was self-reported in 75%-60% of patients across treatment on the PROMIS-CF. Cognitive impairment on neuropsychological tests (AVLT and COWAT) was observed in 9%-3.6% of patients across treatment. There was no increase in cognitive impairment across all measures regardless of prior treatment history or time. Only symptoms of depression and anxiety were associated with PROMIS-CF scores across treatment, $F\ (1,67) = 51.51$, $p = .00$; $F\ (1, 52) = 17.21$, $p = .00$.

Conclusion: CLL patients show similar rates of CRCI as other cancer groups. These findings suggest CLL patients are not at increased risk for cognitive impairment at pre-treatment

assessment and across time. Further research is necessary to validate the findings of this novel study.

Introduction

Cancer and cancer treatment have been associated with cognitive impairment in patients. This impairment, termed cancer-related cognitive impairment (CRCI), is colloquially referred to as "chemo brain" or "chemo fog" (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Janelsins et al., 2011; Bender & Thelen, 2013; Pendergrass, Targum, & Harrison, 2018). It manifests in deficits of executive function, attention, learning and memory, and processing speed. These dysfunctions are associated with reduced quality of life and negatively impact daily functioning. Etiology remains unclear and is suggested to be a consequence of multi-faceted interactions of malignancy, treatment exposure, and biopsychosocial risk factors (e.g. age, stress, depression, fatigue) (Jean-Pierre, Johnson-Greene, & Burish, 2014). Currently, prevalence rates and symptomology reported vary across studies. An estimated 30% of patients pre-treatment, 75% during treatment, and 35% upon competition of treatment report cognitive impairment (Harrington, Hansen, Moskowitz, Todd, & Feuerstein, 2010; Wefel, Vardy, Ahles, & Schagen, 2011). This discrepancy may be due to a variety of factors including heterogenous conceptual definitions of cognitive impairment, cross-sectional study design, lack of control groups and individual pre-treatment cognitive assessment, and variance in diagnostic cut-off points on cognitive measures which limits comparison across studies (Dietrich, Monjie, Wefel, & Meyers, 2008; Wefel et al., 2011; Pendergrass, Targum, & Harrison, 2018). The goal was to study CRCI in patients with chronic lymphocytic leukemia, using a prospective longitudinal design utilizing self-report and objective cognitive assessments: Patient-Reported Outcomes Measurement Information System – Cognitive Function (PROMIS-CF), NIH Auditory Verbal Learning Test (AVLT), and the Controlled Oral Word Association Test (COWAT).

Subjective and objective assessment of CRCI

Presently, CRCI lacks a standardized, gold standard, neuropsychological battery. Variance in CRCI literature is in part due to a failure for studies to specify domains of cognition, subjective or objective, being assessed. Subjective cognition consists of patient-reported or perceived cognitive abilities. Objective cognition infers performance on neuropsychological examinations as indicative of actual or true cognitive abilities. It is widely accepted that commonly used subjective and objective assessments do not converge and are postulated to capture different aspects of cognition (Braun, Rao, & Pirl, 2012; Jean-Pierre et al., 2014; Lycke et al., 2017; O'Farrell, Smith, & Collins, 2017). In a systematic review, researchers found, only 8 out of 24 studies reported a significant relationship between subjective CRCI and objective CRCI across cancer groups (Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012). In a meta-analysis of breast cancer patients, researchers found objective cognition was not associated with subjective cognition, fatigue, mood, or health-related quality of life (Cheung, Tan, & Chan, 2012). On the contrary, subjective CRCI has been associated with fatigue at pre-treatment and across time along with mood (Lycke et al., 2017). It has been suggested that only objective verbal memory scores may be sensitive enough to be associated with subjective cognitive impairment and fatigue on the European Organization for Research and Treatment of Cancer – quality of life questionnaire (EORTC-QLQ) (Mehnert et al., 2007).

Subjective CRCI or perceived cognitive impairment is assessed using self-report questionnaires and/or clinical interview. Subjective impairment has a high prevalence amongst patients and is associated with impairment in daily functioning such as employment and social functioning (Cheung et al., 2012). Self-reported cognitive difficulties have been identified as a significant stressor amongst patients and associated with poorer quality of life in both patients and survivors (Hutchinson et al., 2012; Jean-Pierre et al., 2014).

In contrast, objective CRCI is regarded as 1 to 2 standard deviations below the normative mean on neuropsychological tests assessing executive function. It is often reported as subtle impairment and permits normal range of cognitive abilities, yet, the prevalence rate of objective CRCI in solid tumor cancer patients ranges from 15% to 50% (O'Farrell et al., 2017). Impaired performance on objective measures can result more intensive neuropsychological assessments and allocation of resources to facilitate cognitive training and restoration in patients (Jean-Pierre et al., 2014; Von, Jansen, & Allen, 2014).

Both cognitive domains are subjected to methodological confounds that should be taken under consideration when selecting and administering measures. It is possible that increased rates of subjective CRCI is a result of patient awareness of potential "chemo brain" or misattribution of pre-existing cognitive deficits to cancer or treatment (Lycke et al., 2017). Subjective measures often lack validated normative data to appropriately compare cancer patients (Janelsins et al., 2011; Hutchinson et al., 2012; Pendergrass et al., 2018). Objective CRCI assessments may be confounded by practice effects, differences between studies on the clinical cut-offs of impairment, and cognitive domains assessed may not be translatable to cognitive impairment patients experience in their day-to-day lives. Conducting objective assessments can be restricted by busy clinical settings and research protocol. Furthermore, evidence suggest objective assessments are not sensitive enough to detect mild cognitive deficits, resulting in the potential for underdiagnoses (Jean-Pierre et al., 2014). Current literature recommends usage of both subjective and objective assessments in current CRCI research to best capture domains of cognitive dysfunction in patients (Wefel et al., 2011; Joly et al., 2015).

CRCI Past Research Findings

Currently, the CRCI literature is dominated by cross-sectional studies of breast cancer patients and survivors treated with adjuvant chemotherapy. Evidence suggest the prevalence of cognitive impairment in breast cancer patients may be determined by the reference or control group utilized (Scilder et al., 2010). When compared to study-specific healthy controls, 13.7 to 45.5% of patients showed impairment versus 1 to 36.6% of patients when compared to published norms. Researchers found that cognitive impairment in breast cancer patients ranged from small to moderate, -0.03 to -0.51 standard deviation below controls (Falleti et al., 2015). A temporal impact of CRCI has been identified such that very mild cognitive impairment has been detected from one to nine years post treatment (Harrington et al., 2010). In one prospective study, when analyzed at a group level, cognitive decline was not detected amongst patients receiving adjuvant chemotherapy. However, at an individual level, 30.5% of patients demonstrated significant impairment post treatment (Wefel et al., 2004). Additionally, evidence supports a potential dose-response or cumulative effect of chemotherapy on patients (Collins et al., 2013). Prospective results, controlling for pre-treatment performance, practice effects, and mood found that patients receiving high-dose chemotherapy showed more cognitive impairment compared to standard-dose patients and controls.

CRCI has been studied in other cancer groups. Gynecological cancer survivors have been reported to have elevated subjective CRCI along with psychological measures of depression and anxiety (Zeng et al., 2017). Compared to healthy controls, survivors reported statistically higher subjective CRCI on the Functional Assessment of Cancer Therapy – Cognitive version (FACCT-Cog). Survivors who had received chemotherapy had higher rates of impairment (30.38%) than survivors of surgery (10.13%) along with greater anxiety and fatigue. Also, CRCI is observed amongst prostate cancer survivors who received androgen-deprivation therapy

(Gonzalez et al., 2015). The risk for cognitive impairment on objective measure was 70% higher in prostate cancer patients compared to controls. Impaired performance has been recorded up to 12 months post treatment. Results from the primary literature of CRCI often lacks generalizability outside of adjuvant chemotherapy in breast cancer due to female gender, unique hormonal profiles, and disease-specific treatment (Hutchinson et al., 2012; Falleti et al., 2015). Regardless, evidence suggests that both subjective and objective CRCI is a prevalent adverse consequence in several cancer groups.

CRCI and age

Age is an established risk factor for normal, cognitive decline yet minimal literature specifically evaluates prevalence of cognitive decline in older cancer patients (Loh, 2016). In cancer patients over 70, cognitive impairment at pre-treatment was associated with decreased survival compared to survival for cognitively intact cancer patients (23 months vs 72 months respectively) regardless of exact age or disease prognosis (Robb, 2010). Cancer survivors over 60 performed worse on the Digit Symbol Substitution Test and reported more issues with memory and confusion than age-matched healthy controls (Williams, Janelsins, Wijngaarden 2016). However, the analysis from the Health and Retirement Study reported that cancer survivors did not have cognitive impairment compared to age-matched non-survivor controls (Porter, 2013). Studies may be limited due to low accrual and high attrition rates amongst older patients. Biological mechanisms of potential CRCI in older cancer patients are unknown and cognitive measures may not be validated for older individuals. Overall, the interaction of age, cancer history, and treatment may be associated with increased risk for cognitive impairment and poor quality of life in patients, suggesting age as an important covariate in future CRCI research.

CRCI and hematological cancers

Limited research has assessed cancer-related cognitive impairment in hematological cancers. In them, however, cognition is an important predictor of patient mortality (Dubruille et al., 2015, Hshieh et al., 2018). Executive function deficits are more common than those of working memory however impairment on the 5-word delayed recall test has been associated with increased mortality in lymphoma and leukemia patients over 75 (Hshieh et al., 2018). In a retrospective study of lymphoma survivors, researchers determined widespread objective CRCI and subjective CRCI amongst survivors when compared to healthy controls (Krolak et al., 2017). Frequency of impairment was greater amongst survivors, particularly females (37% compared to 5% for males). Like prior CRCI literature, fatigue and anxiety were associated with subjective CRCI while reported pain was associated with objective CRCI. One study of acute myelogenous leukemia and myelodysplastic syndrome patients evaluated cognitive function, quality of life, and cytokine levels pre-treatment and after one month of chemotherapy (Meyers, Albitar, & Estey, 2005). Results showed, cognitive impairment and significant fatigue pre-treatment were not correlated, but were with correlated increased cytokine levels. Twenty-five percent of patients had difficulties with executive function, suggesting that increased immune activation negatively impacts cognition. Chronic myeloid leukemia patients receiving allogeneic hematopoietic stem cell transplantation saw an increase in impairment on at least one neuropsychological assessment from baseline to 18 months. (Williams et al., 2016). In summary, the few studies conducted with hematologic patients have reported CRCI amongst them compared to controls. Further research into other prevalent non-solid tumor cancers is warranted.

Chronic lymphocytic leukemia (CLL)

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western hemisphere (Nabhan & Rosen, 2014). Regarded as an illness of immune dysfunction; pathology presents an accumulation of abnormal, malignant lymphocytes (Rai et al., 1975; Byrd, Stilgenbauer, & Flinn, 2004). Standard diagnostic techniques involve a blood test, bone marrow biopsy, and measurement of lymph nodes. Risk factors include age (approximately 66% of diagnoses are in individuals over 60), sex, ethnicity, and genetic polymorphisms. Symptomology commonly reports fatigue, weakness, and enlarged lymph nodes. There is variance in disease progression and symptomology, such that some patients show similar survival rates to age-matched healthy controls. CLL treatment is non-curative; treatment aims to slow the rate of abnormal lymphocytosis amongst intermediate or advance staged patients. Temporary remission is often followed by relapse and additional treatment (Nabhan, Raca, & Wang, 2015). Patients who become refractory to frontline treatment typically have a worse prognosis, limited treatment options, and are at risk for increased mortality compared to responsive patients (Fischer et al., 2011). Additional treatment regimens are offered after consideration of patient's expected survival, age, and the potential short and long-term toxicities associated with later treatments (Byrd et al., 2004). Though much of CRCI research focuses on the detriments of chemotherapy, little research has examined the possible cognitive effects of immunotherapies.

CRCI in CLL

Only four studies have examined subjective cognition only using the EORTC QLQ-30 cognitive functioning subscale (Williams et al., 2016). Patients, in treatment and in remission, scored significantly lower than published normative means and healthy controls across studies (Holzner et al., 2004; Else et al., 2008; Pamuk et al., 2008). Previously treated chemotherapy CLL patients performed better than previously untreated patients (77.1 vs. 72.5, $p>0.05$) (Holzner et al.,2004). A cross-sectional study in the Netherlands reported patients actively receiving treatment for CLL were significantly more impaired than non-treated patients (Holtzer et al., 2015).

Current study

No study has assessed objective cognition or cognitive change through treatment in CLL patients. CLL patients commonly report cancer-specific fatigue, and symptoms of depression and anxiety (Morrison et al., 2016). Older CLL patients have greater risk for negative chemotherapeutic side effects than younger CLL patients (Roswell-Turner & Barr, 2017). These factors have been associated with increased risk of cancer-related cognitive impairment (Dietrich et al., 2008; Hutchinson et al., 2012; Joly et al., 2015).

The current study evaluates subjective and objective cognition from pre-treatment to 12 months in CLL patients receiving a novel combination of immunotherapeutic agents (Obinutuzumab, Venetoclax, and Ibrutinib). Differences between patients with no prior treatment history (Treatment Naïve, TN) and at least one prior treatment (Relapse/Refractory, R/R) are assessed. Covariates of interest (e.g. age, and symptoms of depression and anxiety) that have been associated with increased risk of CRCI are assessed in exploratory analyses. Longitudinal study design, cognitive measures, and statistical analyses are in accordance with the International Cancer and Cognition Task Force recommendations for cancer-related cognitive impairment research (Wefel et al., 2011). This study hypothesizes:

1) At pre-treatment, R/R patients will have more cognitive impairment such that R/R will have lower objective scores and higher rates of subjective complaints than TN patients.
2) Across time, both R/R and TN patients will experience more cognitive impairment across all measures.

3) R/R patients will have more cognitive impairment with time compared to TN patients.

Exploratory analyses will assess covariates such as age, and symptoms of depression and anxiety for potential moderating effects between treatment cohorts across measures and time.

Method

Study Design

A phase II clinical trial assessing the efficacy of the novel combination of immunotherapeutic agents (Obinutuzumab, Venetoclax, Ibrutinib) for CLL patients at The James Comprehensive Cancer Center at The Ohio State University (OSU) was utilized. Inclusion criteria included individuals ≥ 18 years of age, without treatment within the past month, and without secondary, significant life-threatening diseases. Prior to enrollment in trial and data collection, informed consent was obtained.

Participants

Forty-four (44) patients with CLL were accrued. Patients were primarily Caucasian (one patient was African American) and 61% were male (n = 27). The average age was 59 (SD = 11) with an average of 15 years of education (SD = 2.7). Patients were in one of two groups. Cohort 1 (n = 23, Treatment Naïve, TN) participants had no prior treatment for their diagnosis of CLL. Cohort 2 (Relapse/Refractory, R/R) participants received at least one prior treatment and either relapsed from a period of remission or failed to respond to initial treatment. There was a significant difference of age between TN patients (M = 59.22; SD=13.83; range = 25-87) and R/R patients (M =59.24; SD =7.20; range = 43-71; $t(42) = -0.06$, p =.01).

Measures

Subjective cognitive. Patient-Reported Outcomes Measurement Information System – Cognitive Function short form (PROMIS-CF) is a self-report questionnaire designed to measure patient-reported complaints with cognition (PROMIS: List of adult measures, 2017). The PROMIS-CF version 2.0 short form subscale consists of eight questions regarding cognitive functioning and distress in daily life. Questions are using a 5-point Likert scale (0=Never to 4=Very Often) in the context of “In the past 7 days”. Items are summed to create a total score and scores range from 0 to 32. The higher the score, the higher perceived cognitive impairment in participants. The PROMIS-CF does not have published normative date for clinical cut offs therefore impairment is assessed as positive endorsement on any question.

Objective cognitive. NIH Toolbox Auditory Verbal Learning Test (AVLT) assesses immediate recall (Kallen et al., 2012). Administrators present a list of 15 random words and participants are prompted to recall as many words as possible. This test was completed three times and participant’s score is the sum of words recalled. Higher scores are associated with better memory and recall abilities. Z-scores were calculated using age and gender norms accessed from the NIH Toolbox technical manual. (Slotkin et al., 2012). The Controlled Oral Word Assessment Test (COWAT) assesses phonemic verbal fluency, spontaneous word generation (Benton, 1994). Administrators prompted participants with a letter (i.e. “F”, “A”, “S”) and provided one minute for participants to generate as many words that began with each corresponding letter. Scores consisted of total of words generated. Higher scores are associated with selective attention, executive control, and the ability of internal response generation. Z-scores were calculated based off age and education norms from 1,300 healthy controls (Tombaugh, Kozak, & Rees, 1999).

Affect. The Patient Health Questionnaire – 9 (PHQ-9) assesses symptoms of depression using a 4-point Likert scale (0 = Not At All to 3 = Nearly Every Day) (Kroenke et al., 2002). Items are totaled and scores range from 0 to 27. Higher scores are associated with increased symptoms of depression. The Generalized Anxiety Disorder – 7 (GAD-7) assesses symptoms of anxiety using a 4-point Likert scale (0 = Not At All to 3 = Nearly Every Day) (Spitzer et al., 2006). Items are totaled and scores range from 0 to 21. Higher scores are associated with increased symptoms of anxiety.

Procedure

Patients were accrued and assessed in a medical oncology clinic, The James Comprehensive Cancer Center at The Ohio State University. Assessments were conducted at pre-treatment, 6 months, and 12 months. This included administration of immunotherapies (Obinutuzumab, Ibrutinib, and Venetoclax) at 6 months and 12 months along with psychometric measures at pre-treatment, 6 months, and 12 months. Psychometric measures were administered by trained researchers, graduate students, and undergraduate research assistants. PROMIS-CF, AVLT, COWAT scores were assessed at pre-treatment, 6 months, and 12 months of treatment. PHQ-9 and GAD-7 scores were assessed at pre-treatment and 12 months of treatment.

Analytic Plan

Statistical analyses were conducted using SPSS 24.0 (IBM, 2016). Descriptive statistics for demographic and clinical characteristics were calculated and independent samples t-tests were used to assess differences between cohorts. Criteria for objective cognitive impairment included a z-score ≤ -1.5 SD on both assessments or a z-score ≤ -2 SD on one assessment. To account for missing data and confounding variables, a linear mixed model was used, a recommended method for repeated measure analyses (Pinheiro & Bates, 2000). Linear mixed model was first conducted to test for the effects of cohort (TN, R/R), time (pre-treatment, 6 months, 12 months) and the interaction of cohort and time. Separate higher order models were conducted controlling for covariates of interest (age followed by PHQ-9 and GAD-7 scores) to test for moderating effects of cohort, time, and interaction of cohort and time.

Results

All participants were included in final analyses despite patient attrition (Figure 1). Independent-samples t-tests showed there were no significant differences between cohorts across gender, years of education, relationship status (Table 1). There were no significant differences between cohorts on all cognitive measure and PHQ-9 or GAD-7 scores at pre-treatment (Table 2). Across cohorts, subjective CRCI was reported in 33 out of 44 (75%) patients at pre-treatment (M = 7.48, SD = 7.91, range = 1-31). At 6 months, 28 out of 40 (60%) patients (M = 6.45, SD = 7.13, range of scores = 1-28) and at 12 months, 18 out of 28 patients (64.3%) (M = 7.29, SD = 8.34, range =1-29) reported some form of cognitive difficulties on the PROMIS-CF. Objective CRCI was less frequently observed. At pre-treatment, 4 out of 44 patients (9%) showed cognitive impairment on either or both objective measures. At 6 months, 3 out of 40 patients (7.5%) and at 12 months, 1 patient out of 28 (3.6%) showed impairment on either or both objective measures.

Subjective cognition

Figure 2 provides a plot of mean PROMIS-CF scores of cohorts across time. Linear-mixed model analyses of PROMIS-CF scores yielded null effects of cohort, time and the interaction of cohort and time on subjective cognition such that PROMIS-CF scores remained constant across cohorts and across treatment. Additional, higher order models containing covariates, PHQ-9 and GAD-7, yielded a statistically significant moderating effect of PHQ-9 score, F (1,67) = 51.51, p = .00, and GAD-7 score, F (1, 52) = 17.21, p = .00 on subjective cognition for both cohorts from pre-treatment to 12 months. The model controlling for age yielded null effects on subjective cognition.

Objective cognition

Figure 3 provides a plot of mean AVLT scores of cohorts across time. Linear-mixed model analyses of AVLT scores yielded significant effects of cohort, F (1, 43) = 3.76, p = .05 and of time, F (1,69) = 3.07, p =.05, while the interaction of cohort and time was null. R/R patients' scores improved while TN patients' scores remained stable across treatment. In additional models containing covariates, there was no main effect of PHQ-9, GAD-7, or age on AVLT scores.

Figure 4 provides a plot of mean COWAT scores of cohorts across time. Linear-mixed model analyses of COWAT scores yielded a significant effect of time, F (2, 66) = 10.75, p = .00, such that both cohorts' scores improved across treatment. Main effect of cohort and interaction of cohort and time were null. In additional models containing covariates, there was no main effect of PHQ-9, GAD-7, or age on COWAT scores.

Discussion

While limited research has assessed subjective and objective CRCI in CLL patients, rates were found to be comparable to those in other cancer groups (Harrington et al., 2010, Wefel et al., 2011, O'Farrell, Smith, & Collins, 2017). Subjective CRCI was reported amongst patients more frequently (75-60%) than objective CRCI (9-3.6%) as reported in prior literature (Hutchinson et al., 2012, Joly et al., 2015).

Results did not support hypothesized adverse effects of prior treatment history on objective performance or rates of cognitive complaints at pre-treatment. Objective CRCI was only found in five patients across time with TN patients displaying a higher frequency of scoring in the impaired direction. Treatment cohorts showed similar rates of subjective complaints at pre-treatment. These findings neither support higher rates of subjective CRCI reported in treatment receiving CLL patients compared to non-treated patients (Holtzer et al.,2015) or lower rates of subjective CRCI in previously treated patients compared to untreated patients (Holzer et al., 2004). Results suggest that R/R patients are not at increased risk for objective or subjective CRCI at pre-treatment assessment. Objective cognition in TN patients should be assessed in further studies to determine potential adverse effects of initial treatment for CLL.

Results did not support hypothesized increase in cognitive impairment across treatment. Both treatment cohorts either improved or remained stable on cognitive measures. TN and R/R patients showed similar improvement on COWAT scores across time. R/R patients improved on AVLT scores while TN patients remained stable from pre-treatment to 12 months. Both cohorts averaged stable rates of cognitive complaints across treatment. Results do not support increased objective CRCI with time as reported in chronic myeloid leukemia patients (Williams et al., 2016). Cognition has not been assessed in CLL patients receiving immunotherapy. These findings suggest this treatment may not associated with increased cognitive impairment across time. Further research assessing both subjective and objective cognition across time amongst CLL patients is needed to validate these findings.

Finally, results did not support a hypothesized interaction of cohort and time such that R/R patients would show more cognitive impairment across treatment compared to TN patients. Treatment history and time impacted objective cognition on AVLT scores such that R/R patients had improved verbal recall abilities across treatment compared to TN patients that remained relatively stable. Across time, COWAT scores improved regardless of treatment history. Subjective cognition was not impacted by treatment history or time. These results do not support the previous CRCI literature which shows increased cognitive impairment across treatment and with increased treatment dosage (Collins et al., 2013). Results suggest that treatment history does not have an adverse effect across treatment such that R/R patients are not at increased risk of subjective or objective CRCI compared to TN patients throughout treatment. Further research is necessary to assess the impact of treatment history in this cancer group.

Constant subjective rates of cognitive complaints across treatment cohorts were not reflected with similar stability of objective performance. Objective cognitive improvement on COWAT scores were recorded in both cohorts. While improvement on AVLT scores were observed amongst R/R patients. These results support prior literature stating subjective and objective cognitive measures do not converge and are assessing different domains of cognition as observed in other cancer groups (Braun et al., 2012; Jean-Pierre et al., 2014; Lycke et al., 2017; O'Farrell et al., 2017).

Furthermore, exploratory analyses of covariates of interest, symptoms of depression and anxiety, supported prior literature that subjective cognition is impacted by self-reported symptoms of depression and anxiety whereas objective cognition is not (Cheung et al., 2012; Lycke et al., 2017). Across cohorts, patients self-reported symptoms of depression and anxiety moderated rates of cognitive complaints. This study does not support literature suggesting that increased age increases risk for cognitive impairment (Williams et al., 2016). These findings suggest that CLL patients are not increased risk of cognitive impairment despite commonly presenting risk-factors.

The current study is the first to assess objective cognition amongst CLL patients. Additionally, subjective and objective cognition were studied longitudinally with the added comparison of prior treatment history. This study's design, measures, and statistical analyses are all in accordance with the International Cognition and Cancer Task Force's recommendations for CRCI research (Wefel et al., 2011).

Limitations of this study include a small patient population which may have hindered the ability to detect statistically significant differences across measures. Potential confounds include risk for practice effect on objective cognitive measures such that improvement on measures may not have been indicative of true cognitive abilities. However, it has been suggested that waiting 6 to 12 months between repeated objective assessment minimizes the potential of practice effects (Jean-Pierre et al., 2014). While pre-treatment assessments were administered prior to immunotherapeutic treatment some patients received anti-histamines prior to or during in-person assessment potentially impacting cognitive abilities. Furthermore, the covariates such as fatigue and general affect were not studied.

Future research might utilize a complete neuropsychological battery along with subjective measures to assess a wider range of cognitive domains and potential impairment. Continued usage of recommended cognitive measures (e.g. PROMIS-CF, AVLT, and COWAT) across cancer groups along with repeated measure analyses is essential to continue throughout future CRCI studies. Increased assessment of cognition in specific cancer populations other than breast cancer patients is necessary to fully comprehend CRCI.

In conclusion, in CLL patients, treatment history did not negatively impact subjective or objective cognitive abilities at pre-treatment or across treatment. CLL patients are not at increased risk for CRCI despite the prevalence of risk factors associated with increased cognitive impairment. Further research is warranted to validate the findings of this novel study of cognition amongst the CLL population.

Table 1
Baseline Patient Demographics Between Treatment Cohorts

	Cohort				
	TN (n = 23)		R/R (n = 21)		
Category	*M (SD)*	N (%)	*M (SD)*	N (%)	*p*
Age (in years)	59.2 (13.83)		59.2 (7.20)		0.01
Gender (Male)		14 (61%)		13 (62%)	0.89
Married/Partnered (Yes)		19 (83%)		18 (86%)	0.58
Education (in years)	15.0 (2.61)		15.4 (2.75)		0.89

Note. TN = treatment naïve (no prior treatment); R/R = relapse/refractory (≥ 1 prior treatment).

Table 2

Descriptive Statistics of Clinical Characteristics of Treatment Cohorts

	Cohort					
	TN[a]		R/R[b]		Total[c]	
Measure	*M*	*SD*	*M*	*SD*	*M*	*SD*
Cognition						
PROMIS-CF						
pre-treatment	7.61	6.65	7.33	9.27	7.48	7.91
6 months	6.04	5.79	7.00	8.79	6.45	7.13
12 months	7.71	8.05	6.64	9.11	7.29	8.34
Total	7.06	6.70	7.06	8.88	7.06	7.70
AVLT						
pre-treatment	0.30	0.76	0.46	0.76	0.38	0.76
6 months	0.37	0.92	1.12	0.95	0.69	1.00
12 months	0.49	0.86	0.76	0.93	0.59	0.88
Total	0.38	0.84	0.76	0.90	0.54	0.88
COWAT						
pre-treatment	-0.30	1.25	-0.43	1.05	-0.36	1.15
6 months	0.08	1.35	0.15	1.15	0.11	1.25
12 months	0.20	1.29	0.18	0.63	0.19	1.06
Total	-0.03	1.29	-0.09	1.03	-0.05	1.18
Affect						
PHQ-9						
pre-treatment	4.17	3.05	3.95	5.03	4.07	4.07
12 months	3.12	4.00	2.64	3.58	2.93	3.78
Total	3.73	3.48	3.50	4.57	3.63	3.97
GAD-7						
pre-treatment	3.26	2.80	3.62	4.17	3.43	3.48
12 months	2.35	2.78	2.00	2.53	2.21	2.64
Total	2.88	2.79	3.43	3.48	2.96	3.22

Note. TN = treatment naïve (no prior treatment); R/R = relapse/refractory (≥ 1 prior treatment);
[a]n = 23 (pre-treatment), 23 (6 months), 17 (12 months); [b]n = 21 (pre-treatment), 17 (6 months), 11 (12 months); [c]n = 44 (pre-treatment), 40 (6 months), 28 (12 months);
PROMIS = patient-reported outcomes measurement information systems - cognitive function;
AVLT = auditory verbal learning test; COWAT = controlled oral word association test;
PHQ-9 = patient health questionnaire - 9; GAD-7 = generalized anxiety disorder - 7

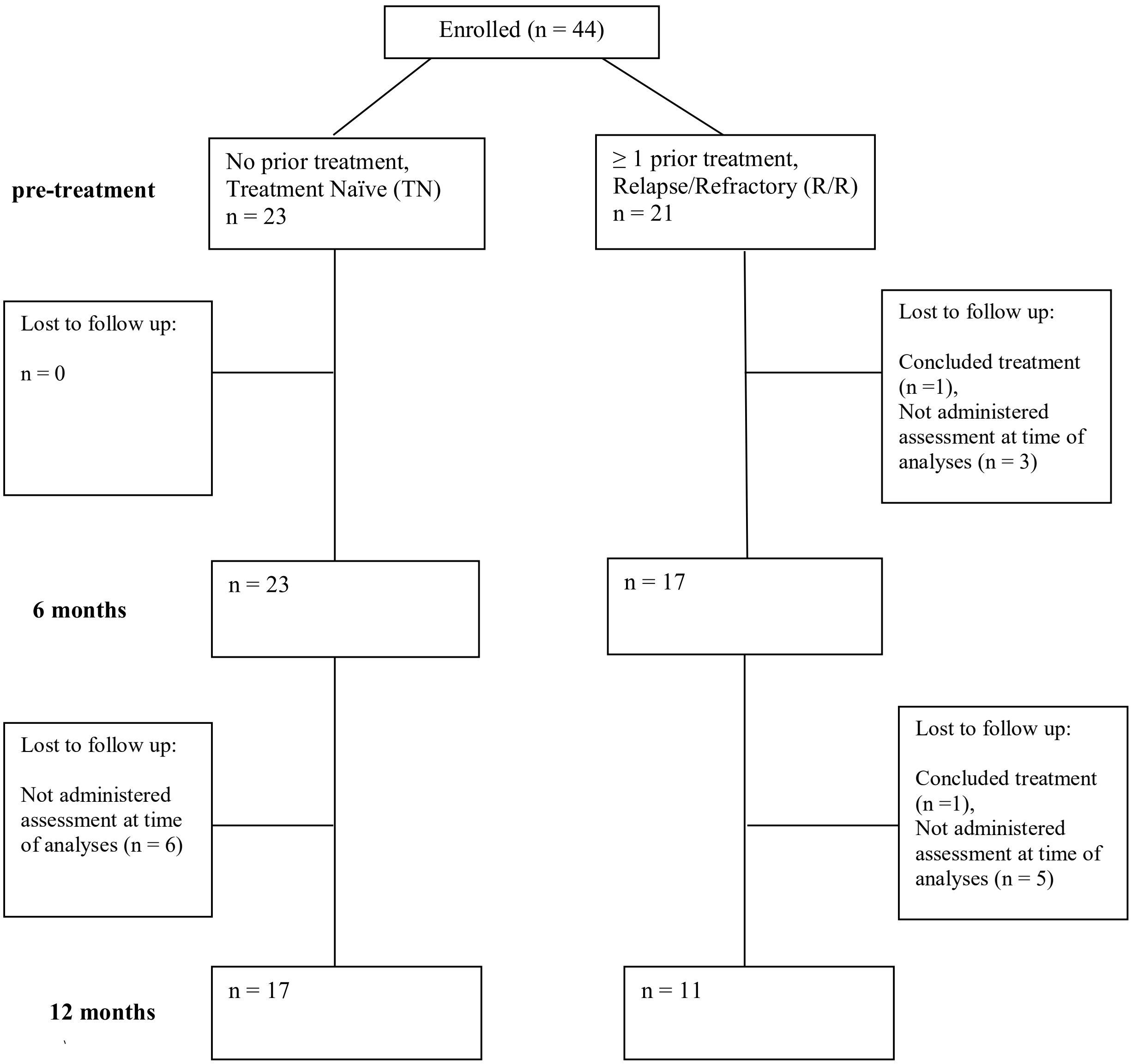

Figure 1. Flow of Participants from pre-treatment through 12 months

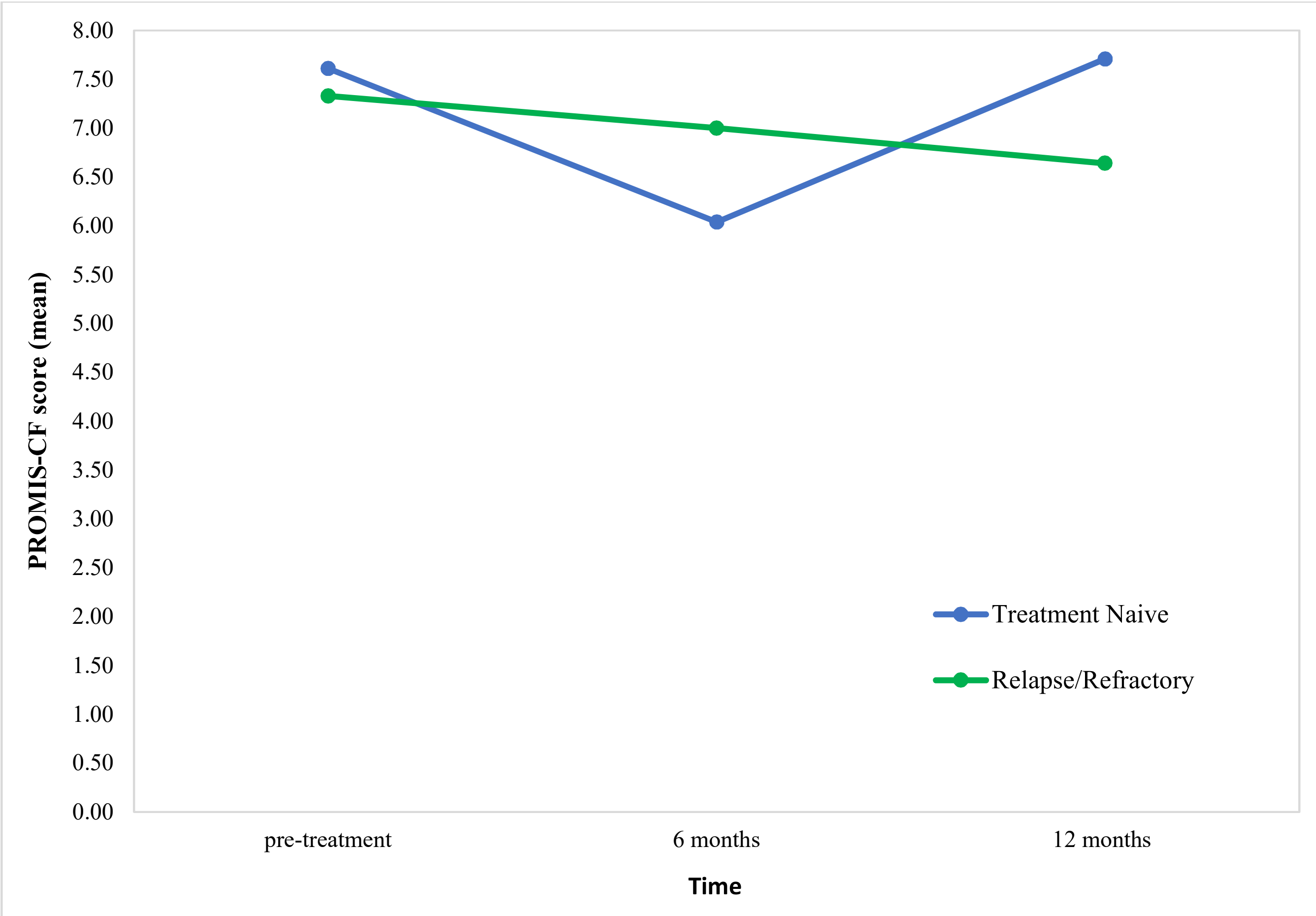

Figure 2. PROMIS-CF score (mean) by treatment cohort showing null effects of cohort, time, and interaction of cohort and time.

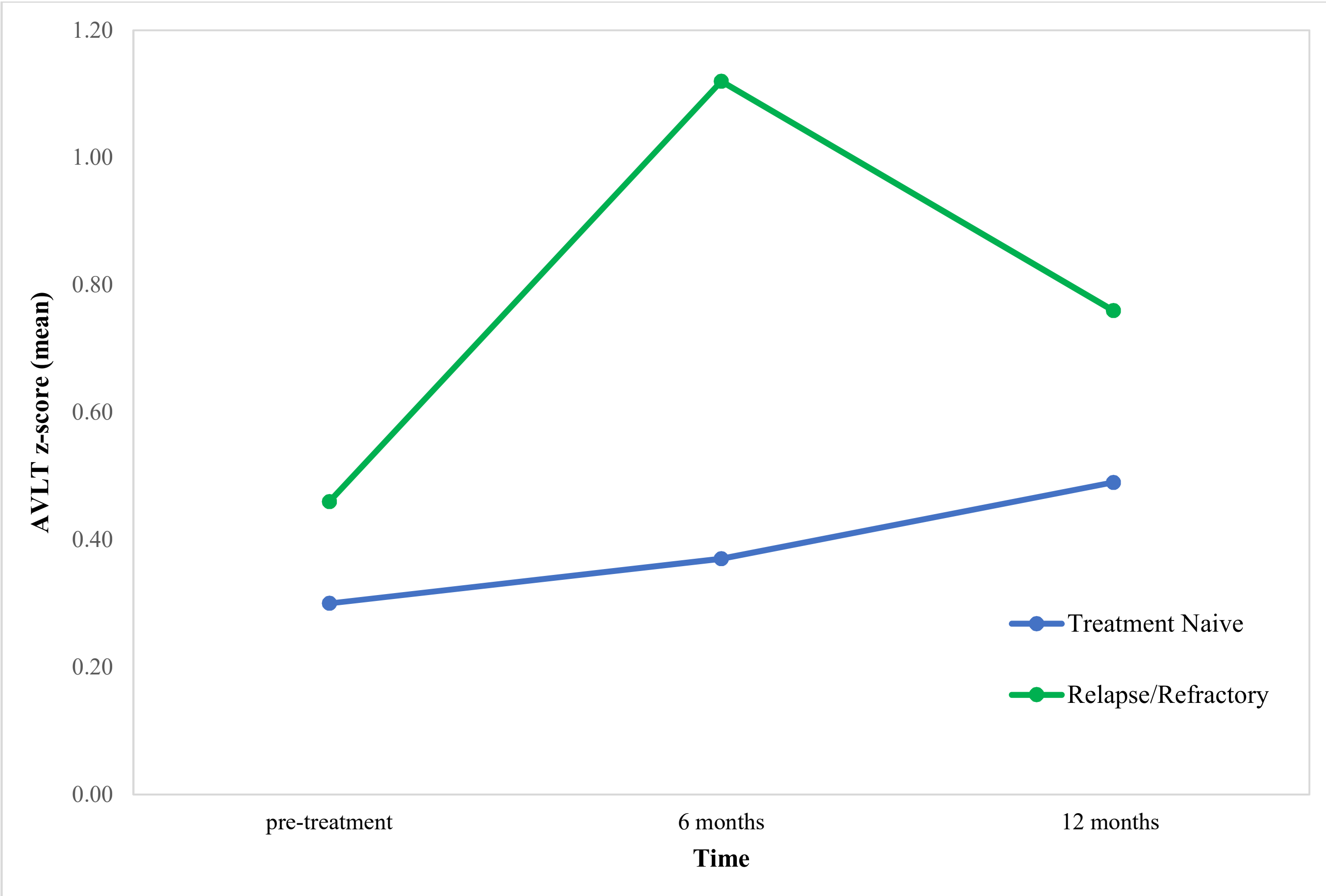

Figure 3. AVLT score (means) of treatment cohorts showing a significant effect of cohort, F (1,43) = 3.76, p = .05, and of time, F (1,69) = 3.07, p = .05 such that Relapse/Refractory patients AVLT scores improved across time compared to Treatment Naïve patients. No significant interaction of cohort and time.

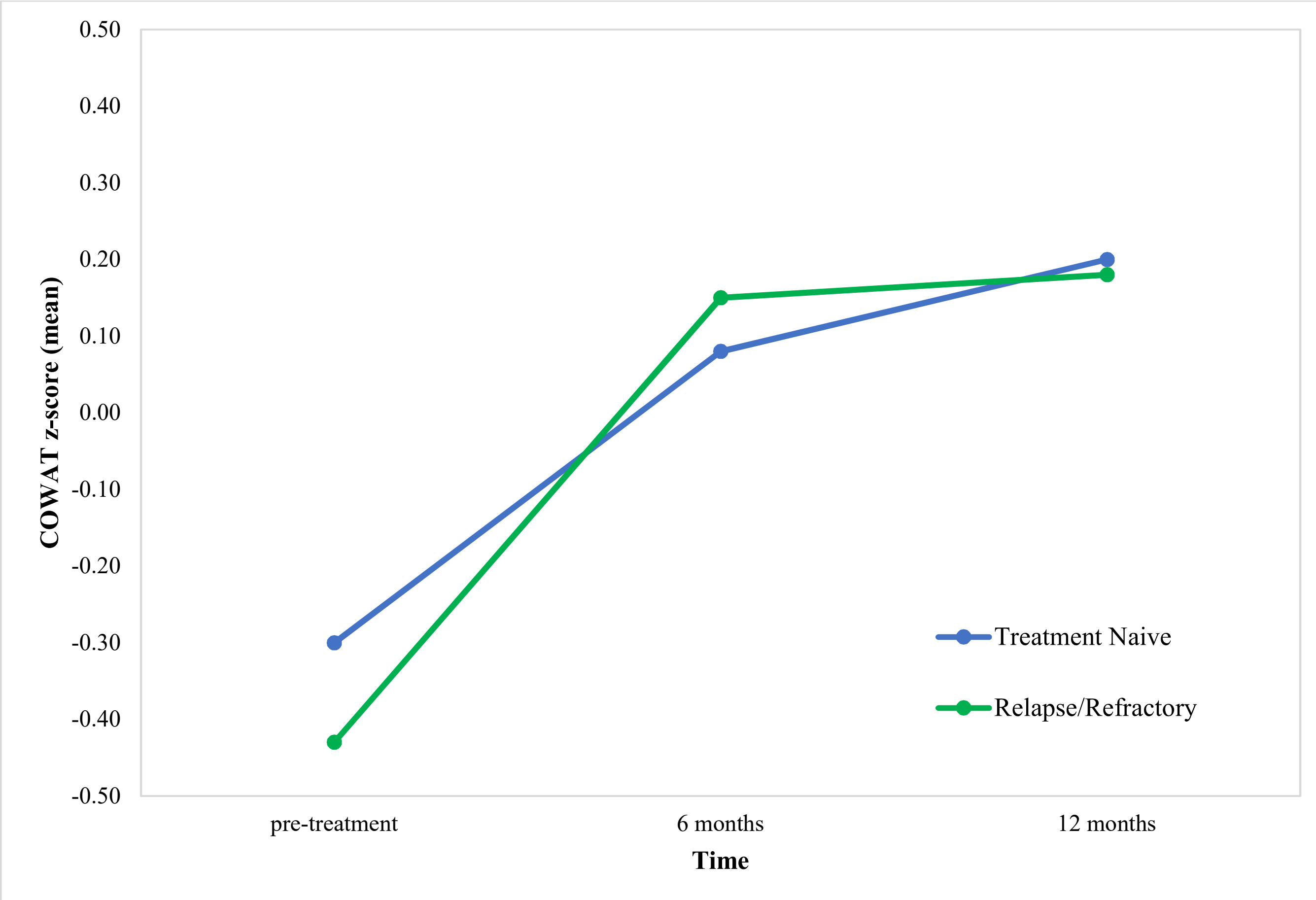

Figure 4. COWAT score (means) of treatment cohorts across showing a significant effect of time, F (2,66) = 10.75, p = .00 such that COWAT scores improved across time in both treatment cohorts. Main effect of cohort and interaction of cohort and time were null.

References

Bender, C. M., & Thelen, B. D. (2013, November). Cancer and cognitive changes: the complexity of the problem. In *Seminars in Oncology Nursing* (Vol. 29, No. 4, pp. 232-237). WB Saunders.

Benton, A. L. (1994). Contributions to neuropsychological assessment: A clinical manual. Oxford University Press, USA.

Braun, I. M., Rao, S. R., & Pirl, W. F. (2012). Comparison of self-reported cognitive difficulties in a national sample of long-term cancer survivors and cancer-naive controls. *Psychosomatics*, *53*(1), 68-74.

Collins, B., MacKenzie, J., Tasca, G. A., Scherling, C., & Smith, A. (2013). Cognitive effects of chemotherapy in breast cancer patients: a dose–response study. *Psycho-Oncology*, *22*(7), 1517-1527.

Dietrich, J., Monje, M., Wefel, J., & Meyers, C. (2008). Clinical patterns and biological correlates of cognitive dysfunction associated with cancer therapy. *The Oncologist*, *13*(12), 1285-1

Else, M., Cocks, K., Crofts, S., Wade, R., Richards, S. M., Catovsky, D., ... & UK National Cancer Research Institute (NCRI) Chronic Lymphocytic Leukaemia Trials Group. (2012). Quality of life in chronic lymphocytic leukemia: 5-year results from the multicenter randomized LRF CLL4 trial. *Leukemia & Lymphoma*, *53*(7), 1289-1298.

Falleti, M. G., Sanfilippo, A., Maruff, P., Weih, L., & Phillips, K. A. (2005). The nature and severity of cognitive impairment associated with adjuvant chemotherapy in women with breast cancer: a meta-analysis of the current literature. *Brain and Cognition*, *59*(1), 60-70.

Fischer, K., Cramer, P., Busch, R., Stilgenbauer, S., Bahlo, J., Schweighofer, C. D., ... & Kranz, G. (2011). Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the german chronic lymphocytic leukemia study group. *Journal of Clinical Oncology*, 29(26), 3559-3566.

Gonzalez, B. D., Jim, H. S., Booth-Jones, M., Small, B. J., Sutton, S. K., Lin, H. Y., ... & Jacobsen, P. B. (2015). Course and predictors of cognitive function in patients with prostate cancer receiving androgen-deprivation therapy: a controlled comparison. *Journal of Clinical Oncology*, 33(18), 2021.

Harrington, C. B., Hansen, J. A., Moskowitz, M., Todd, B. L., & Feuerstein, M. (2010). It's not over when it's over: long-term symptoms in cancer survivors—a systematic review. *The International Journal of Psychiatry in Medicine*, *40*(2), 163-181

Holzner, B., Kemmler, G., Kopp, M., Nguyen-Van-Tam, D., Sperner-Unterweger, B., & Greil, R. (2004). Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr. *European Journal of Haematology*, *72*(6), 381-389.

Holtzer-Goor, K. M., Schaafsma, M. R., Joosten, P., Posthuma, E. F. M., Wittebol, S., Huijgens, P. C., ... & Erjavec, Z. (2015). Quality of life of patients with chronic lymphocytic leukaemia in the Netherlands: results of a longitudinal multicentre study. *Quality of Life Research*, *24*(12), 2895-2906.

Hshieh, T. T., Jung, W. F., Grande, L. J., Chen, J., Stone, R. M., Soiffer, R. J., ... & Abel, G. A. (2018). Prevalence of cognitive impairment and association with survival among older patients with hematologic cancers. *JAMA Oncology*.

Janelsins, M. C., Kohli, S., Mohile, S. G., Usuki, K., Ahles, T. A., & Morrow, G. R. (2011, June). An update on cancer-and chemotherapy-related cognitive dysfunction: current status. *Seminars in Oncology* (Vol. 38, No. 3, pp. 431-438). Elsevier.

Jean-Pierre, P., Johnson-Greene, D., & Burish, T. G. (2014). Neuropsychological care and rehabilitation of cancer patients with chemobrain: strategies for evaluation and intervention development. *Supportive Care in Cancer*, 22(8), 2251-2260.

Kallen, M., Slotkin, J., Griffith, J., Magasi, S., Salsman, J., Nowinski, C., & Gershon, R. (2012). NIH Toolbox.

Pamuk, G. E., Harmandar, F., Ermantaş, N., Harmandar, O., Turgut, B., Demir, M., & Vural, Ö. (2008). EORTC QLQ-C30 assessment in Turkish patients with hematological malignancies. *Annals of Hematology*, *87*(4), 305-310.

Pendergrass, J. C., Targum, S. D., & Harrison, J. E. (2018). Cognitive Impairment Associated with Cancer: A Brief Review. *Innovations in Clinical Neuroscience*, 15(1-2), 36.

Pinheiro, J. C. (2000). Mixed-Effects Models in S and S-PLUS, José C. Pinheiro and Douglas M. Bates. Statistics and Computing Series. Springer-Verlag, New York, NY, 2000.

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of Internal Medicine*, 166(10), 1092–1097.

Tombaugh, T. N., Kozak, J., & Rees, L. (1999). Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Archives of Clinical Neuropsychology,* 14(2), 167-177.

Valpey, R. E. (2017). Cancer-Related Cognitive Impairment: Considering Risk Factors, Approaching Assessment, and Contemplating Treatment.

Von Ah, D., Jansen, C. E., & Allen, D. H. (2014). Evidence-based interventions for cancer-and treatment-related cognitive impairment. *Clinical Journal of Oncology Nursing*, *18*.

Wefel, J. S., Lenzi, R., Theriault, R. L., Davis, R. N., & Meyers, C. A. (2004). The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: Results of a prospective, randomized, longitudinal trial. *Cancer*, 100, 2292–2299.

Wefel, J. S., Vardy, J., Ahles, T., & Schagen, S. B. (2011). International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *The Lancet Oncology*, *12*(7), 703-708.295.

Weintraub, S., Dikmen, S. S., Heaton, R. K., Tulsky, D. S., Zelazo, P. D., Slotkin, J., ... & Havlik, R. (2014). The cognition battery of the NIH toolbox for assessment of neurological and behavioral function: Validation in an adult sample. *Journal of the International Neuropsychological Society*, 20(6), 567-578.